REMARKS

By amendment, claims 1-11 are cancelled and new claims 12-22 are added. Support for the new claims can be found in the original claims, and in the specification as filed, particularly page 7, fourth paragraph; pages 11-12, bridging paragraph; pages 8-9, bridging paragraph; page 15, paragraphs 3, 4, and 5; page 16, first paragraph; and page 18, first paragraph.

Abstract

The Examiner objects to the abstract because "the present claims are not directed to preparation of a medicament" (Office Action, page 2). By amendment, the phrase "preparation of a medicament" is removed from the abstract, and the subject matter of treatment of cancer is added. Applicants request withdrawal of the objection to the abstract.

35 U.S.C. § 101 / 35 U.S.C. § 112, second paragraph

Claim 1 is rejected for reciting a "use without any active, positive steps delimiting how this use is actually practiced" (Office Action, page 2). Applicants respectfully traverse. However, the rejection is rendered moot, since by amendment, claim 1 is cancelled. New claims 12-22 are directed to methods of treatment of a human patient for cancer comprising the active positive step of administering Et 743.

35 U.S.C. § 102(b)

Claims 1-3, 5, and 9 are rejected as being anticipated by Drugs Fut. The Examiner states that the "reference teaches the administration of a formulation comprising ET-473 for intravenous administration to treat human cancers such as chemoresistant ovarian carcinoma, as

well as lung, melanoma and renal cancer." (Office Action, page 3). Applicants respectfully traverse. However, to advance prosecution, by amendment, claims 1-3, 5, and 9 are cancelled. The following arguments are presented with respect to new claims 12-22.

By amendment, new independent claim 12 requires that Et 743 is administered by intravenous infusion at intervals of about 1-6 weeks with an infusion time of about 2-24 hours. The Drugs Fut. reference does not teach or suggest that such administration cycles may provide an effective treatment of cancer in the human body. The reference discusses a number of in vitro studies of Et 743 on certain tumor cell lines. The reference then discusses treatment of human tumor xenografts in mice. A number of different doses are given, including a single dose, intravenous administration at 4 day intervals, and a 5 day administration in 3 cycles at 31 days apart. None of these administration cycles comprise administering Et 743 in cycles by intravenous infusion at intervals of about 1-6 weeks with an infusion time of about 2 to about 24 hours. Therefore, the reference does not anticipate the claimed methods of treatment of a human patient for cancer. Applicants request withdrawal of the rejection.

35 U.S.C. § 102(a)

Claims 1-9 are rejected as being anticipated by Izbicka et al., Annals of Oncology. The Examiner states that the reference "teaches the administration of ET-743 against various human tumors. See Tables 1a and 1b, pages 983 and 984." (Office Action, page 3). The Examiner further points to pages 985, column 2, and pages 985-986, stating that "ET-743 may inhibit the growth of some tumors resistant to other drugs." (Office Action, page 3). Applicants respectfully traverse. However, to advance prosecution, by amendment, claims 1-9 are cancelled. The following arguments are presented with respect to new claims 12-22.

By amendment, new independent claim 12 requires that Et 743 is administered by intravenous infusion at intervals of about 1-6 weeks with an infusion time of about 2-24 hours. The Annals of Oncology reference does not teach or suggest that such administration cycles may provide an effective treatment of cancer in the human body. The reference discusses results obtained from in vitro studies on tumor cells. Such results do not provide the information necessary for an effective dosing protocol. Further, the reference discusses the exposure of tumor cells to Et 743 either for a single administration of one hour, or for a continuous 14 day administration. None of these administration cycles comprise administering Et 743 in cycles by intravenous infusion at intervals of about 1-6 weeks with an infusion time of about 2 to about 24 hours. Therefore, the reference does not anticipate the claimed methods of treatment of a human patient for cancer. Applicants request withdrawal of the rejection.

35 U.S.C. § 103(a)

Claims 1-11 are rejected as being unpatentable over by Izbicka et al., Annals of Oncology. The Examiner states that the reference "teaches the administration of ET-743 against various human tumors. See Tables 1a and 1b, pages 983 and 984." (Office Action, page 4). The Examiner further states that "Fifteen tumor types are disclosed" and that both one hour and continuous exposure through intravenous administration are disclsoed (Office Action, page 4). The Examiner admits that the claims differ with respect to dosing regimens, but argues that one skilled in the oncology art would have been motivated to select particular dosages in view of Izbicka's teaching. The Examiner argues that

> "Such would have been obvious in the absence of evidence to the contrary because Izbicka recites a maximum tolerated dose of 600 μg/m2, as well as one hour exposures and continuous exposures (24 hours). Multiple cycles of 3-4 weeks are conventional

> chemotherapeutic practices. The determination of safe and effective dosages with the occurrence of minimal adverse effects is a parameter well within the purview of those skilled in the oncology art through no more than routine experimentation" (Office Action, page 4).

Applicants respectfully traverse. However, to advance prosecution, by amendment, claims 1-11 are cancelled. The following arguments are presented with respect to new claims 12-22.

By amendment, new independent claim 12 requires that Et 743 is administered by intravenous infusion at intervals of about 1-6 weeks with an infusion time of about 2-24 hours. The Annals of Oncology reference does not teach or suggest that such administration cycles may provide an effective treatment of cancer in the human body. The reference discusses results obtained from in vitro studies on tumor cells. Such results do not provide the information necessary for an effective dosing protocol. Further, the reference discusses the exposure of tumor cells to Et 743 either for a single administration of one hour, or for a continuous 14 day administration. None of these administration cycles comprise administering Et 743 in cycles by intravenous infusion at intervals of about 1-6 weeks with an infusion time of about 2 to about 24 hours. The Examiner admits that the claims differ with respect to dosing regimens.

With respect to motivation to select particular dosages, and that such "would have been obvious in the absence of evidence to the contrary," Applicants note that the Drugs Fut. reference cited above shows that the 5-day infusion was observed to have a high level of lethality. The reference teaches away from the use of Et 743 in stating that "the drug's toxicity is cumulative and apparently irreversible. Thus the drug may not be useful in a clinical setting" (Drugs Fut., page 1279, column 1, fourth paragraph). The Examiner has narrowly focused on the Annals of Oncology reference and improperly disregarded prior art references that teach away from the instant invention. Based on this evidence to the contrary, the skilled person would not

be led to consider that Et 743 would provide a safe and effective treatment of cancer at all, let alone with the specific administration cycles required in claim 12.

Further, it is noted that the Annals of Oncology reference, rather than teaching exposure for 24 hours as asserted by the Examiner, actually teaches 14-day continuous exposure (see page 983, column 1, last paragraph). Results of the 14-day continuous exposure experiments teach away from the present claims, which recite a limited infusion time of about 2 to 24 hours. In addition, these findings appear to contradict the findings of the Drugs Fut. article, which suggested that a 5-day administration was lethal. Therefore, one cannot arbitrarily arrive at the claimed invention absent the use of hindsight reconstruction.

The Examiner suggests that "multiple cycles of 3-4 weeks are conventional chemotherapeutic practices," but fails to provide any prior art references to support the assertion. In addition, the Examiner suggests that the determination of safe and effective dosages is well within the purview of those skilled in the oncology art through no more than routine experimentation. The Annals of Oncology reference suggests otherwise, stating at the foot of the first column on page 985 that "not all minor groove binders follow the same schedule clinically." In other words, an effective clinical dosage schedule is unpredictable in the art. Therefore, even if the skilled person were to proceed against the teachings of the Drugs Fut. reference and consider that Et 743 would be useful in a clinical setting, and were also to proceed against the teaching of the Annals of Oncology reference by considering using shorter dosage times than the 14 day exposure which is stated as being desirable, there would still be nothing in the prior art which would lead the skilled person to the dosage schedule as currently claimed. Therefore, the Annals of Oncology reference does not render obvious the claimed methods of treatment of a human patient for cancer. Applicants request withdrawal of the rejection.

Information Disclosure Statement

Attached is an Information Disclosure Statement and PTO Form 1449. This Information Disclosure Statement is filed in accordance with 37 C.F.R. §§1.56, 1.97 and 1.98. The items listed on Form PTO-1449, a copy of which is enclosed, are made of record to assist the Patent and Trademark Office in its examination of this application. The Examiner is respectfully requested to fully consider the items and to independently ascertain their teaching, as indicated by return of a copy of Form 1449 with the Examiner's initials and signature.

As cited in the IDS, Applicants respectfully direct the Examiner's attention to the "Summary of Opinion" by the European Agency for the Evaluation of Medicinal Products (EMEA). Yondelis™ is the tradename for Et 743.

The Examiner's attention is further directed to two press releases by Pharma Mar, each cited in the IDS. The November 20, 2003 press release states that the "leading European experts in STS [soft tissue sarcoma] support Yondelis and believe that the drug should be made available immediately to STS patients who today have no alternative therapy," (November 20, 2003 press release, 2nd paragraph).

CONCLUSION

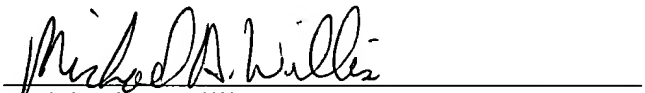
Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. 13-4500, Order No. 4126-4007. A DUPLICATE OF THIS DOCUMENT IS ATTACHED.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 4126-4007. A DUPLICATE OF THIS DOCUMENT IS ATTACHED.

Respectfully submitted,
MORGAN & FINNEGAN, L.L.P.

Dated: August 25, 2004 By: 

Michael A. Willis
Registration No. 53,913

Correspondence Address after August 2, 2004
MORGAN & FINNEGAN, L.L.P.
3 World Financial Center
New York, New York 10281-2101
Tel: (212) 415-8700
Fax: (212) 415-8701